BRAVO I: A pilot study of vascular brachytherapy in polytetrafluoroethylene dialysis access grafts

S Misra[1], R Bonan[2], T Pflederer[3] and P Roy-Chaudhury[4] for the BRAVO I Investigators

[1]*Department of Radiology, Cardiology and Surgery, Mayo Clinic, Rochester, Minnesota, Minnesota, USA;* [2]*Department of Cardiology, Montreal Heart Institute, Montreal, Canada;* [3]*Renal Care Associates, Morton, Illinois, USA and* [4]*Division of Nephrology, University of Cincinnati, Cincinnati, Ohio, USA*

Hemodialysis vascular access dysfunction owing to stenosis and thrombosis in polytetrafluoroethylene dialysis access grafts is a huge clinical problem for which there are currently no long lasting durable therapies. Vascular brachytherapy has been used successfully for the prevention of coronary restenosis following angioplasty and stent placement. The Beta Radiation for Treatment of Arterial-Venous Graft Outflow I study was a pilot study of vascular brachytherapy in hemodialysis patients with patent but dysfunctional grafts. Twenty-five patients were randomized to receive either radiation therapy (a single dose of 18.4 Gy) or sham radiation, following angioplasty. The primary efficacy end point of the study was target lesion primary patency at 6 months. The primary safety end point was a composite of death, emergency surgery on the graft, venous rupture, or aneurysm formation. Forty-two percent of the radiated grafts achieved the target lesion primary patency end point at 6 months as compared to 0% of the control group ($P = 0.015$), but this did not translate into an improvement in secondary patency at either 6 or 12 months. Radiation therapy was found to be safe in the setting of hemodialysis vascular access dysfunction. Our results suggest that vascular brachytherapy is an intervention that is worthy of further examination in the setting of non-thrombosed dialysis access grafts.

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Correspondence: *P Roy-Chaudhury, Division of Nephrology, University of Cincinnati, MSB G251, 231 Albert Sabin Way, Cincinnati, Ohio 45267-0585, USA. E-mail: prabir.roychaudhury@uc.edu*

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Hemodialysis vascular access dysfunction is currently an important cause of morbidity and hospitalization in the hemodialysis population (approximately 300 000 patients in the United States).[1] The vast majority of hemodialysis vascular dysfunction is due to venous stenosis followed by thrombosis in polytetrafluoroethylene (PTFE) dialysis access grafts which comprise approximately 40% of all permanent dialysis access in the United States, although some regions have a higher prevalence.[2,3] *At a cellular level*, venous stenosis in the setting of PTFE dialysis grafts is due to venous neointimal hyperplasia, which is characterized by smooth muscle cell/myofibroblast proliferation and migration, microvessel formation, or angiogenesis within the venous neointima and the presence of a macrophage layer lining both surfaces of PTFE graft.[4–8] *At a clinical level*, PTFE dialysis grafts have a dismal primary patency (as low as 23% at 1 year and 4% at 2 years in some studies) and require an average of 1.22 procedures/year (greater than 200 000 annually) in order to maintain patency (0.54 angioplasties, 0.51 thrombectomies, and 0.17 surgical revisions per patient year).[9] Unfortunately the results following angioplasty of dialysis access grafts are very poor with only a 40%, 3-month primary patency for thrombosed PTFE dialysis grafts and a 50%, 6-month patency for patent but dysfunctional grafts.[10,11] Consequently hemodialysis vascular access dysfunction has been estimated to have an economic cost of over one billion dollars per annum or $8000 per annum for each at risk patient.[12–14] This is in addition to a huge negative impact on the quality of life of hemodialysis patients, who already have multiple co-morbidities. Despite the magnitude of the clinical problem, however, there are currently no long lasting and durable therapies for the prevention or treatment of hemodialysis vascular access dysfunction.[2]

Radiation therapy has been shown at an *in vitro* level to inhibit the proliferation of all three cell types involved in the lesion of venous stenosis in PTFE dialysis grafts (smooth muscle cells, macrophages, and endothelial cells in microvessels).[15–17] At an experimental level vascular brachytherapy (endovascular radiation therapy) can inhibit post-angioplasty coronary restenosis.[18,19] In addition experimental studies in pig models of arteriovenous graft stenosis have demonstrated a reduction in neointimal hyperplasia and luminal stenosis

with external beam,[20] and endovascular[21] radiation therapy. Finally at a clinical level, numerous reports have documented a significant decrease in coronary restenosis following vascular brachytherapy.[22–24] The most relevant clinical information (from coronary studies) with regard to venous stenosis in PTFE dialysis grafts, however, comes from the SVG WRIST study[25] which was able to demonstrate a beneficial effect of vascular brachytherapy in the setting of saphenous *vein* graft stenosis. Additional data on the feasibility and safety of using vascular brachytherapy clinically for venous stenosis comes from a subset analysis of the RENO trial.[26] In terms of current cardiology clinical practice, however, vascular brachytherapy is not as effective as drug eluting stents for the prevention of restenosis following angioplasty and stent placement.[27,28] More recently, studies have demonstrated that placement of a drug eluting stent is superior to vascular brachytherapy, even in the setting of restenosis of a bare metal stent.[29,30] Drug eluting stents, however, are currently not available for clinical use in patients with hemodialysis vascular access dysfunction.

Despite the significant experimental and clinical data supporting the use of radiation therapy for vascular stenosis, there is a surprising paucity of data on the use of radiation therapy in the setting of dialysis access stenosis. Before the current study, the only data available for vascular brachytherapy following angioplasty of dialysis access grafts was a small nonrandomized study from the Emory Clinic which demonstrated the safety of this procedure.[31] In addition Cohen *et al.*[32] have published on a small randomized study of external beam radiation therapy, following dialysis access stenosis. This study demonstrated a trend towards a better outcome in the radiation group although this was not statistically significant. Unfortunately, the study group was very heterogenous and included PTFE grafts, primary arteriovenous fistulae, and brachiobasilic transpositions.

We report herein on the BRAVO I (Beta Radiation for Treatment of Arterial-Venous Graft Outflow) trial, which was a randomized pilot study of vascular brachytherapy therapy for patent (non-thrombosed) but dysfunctional PTFE dialysis access grafts.

RESULTS

Sixty-five patients agreed to participate in the BRAVO 1 trial from nine different institutions. Forty patients did not qualify for the trial (screen failures), primarily because they failed to meet the angiographic inclusion and exclusion criteria such as the requirement for an absence of tandem stenoses, or the need for a 50% stenosis at the graft-vein anastomosis (see Table 3). Thus 25 patients from six different institutions (see Appendix A) were randomized to either Radiation ($n = 14$) or sham radiation (Controls; $n = 11$). 2 patients died before a 6-month angiogram. Both patients were in the Radiation group. The causes of death were myocardial infarction and sepsis. Both deaths were thought to be unrelated to the study treatment. These patients have not been included in the outcome results as they did not have the 6-month angiogram needed for the primary efficacy endpoint. Both patients appeared to have functioning grafts at the time of death. In addition, two other patients in the study died after completion of the 6-month angiogram, one each in the Radiation and Control groups. The cause of death in both these patients was thought to be sepsis.

Demographics and vascular access history

Table 1 shows the demographics of the Radiation and Control groups. In keeping with the current demographics of hemodialysis patients in the United States, the mean age for both groups was 64 years with diabetes mellitus being the leading cause of end-stage renal disease. African Americans constituted 36% of the total study population. Table 2 describes the location (forearm versus upper arm) and configuration (straight versus loop) of the current hemodialysis graft and also the number of previous accesses. Both groups appeared similar albeit with more loop grafts in the Radiation group. In addition, there were no differences between the two groups with respect to dialysis adequacy (*Kt/V* and urea reduction ratio).

Table 1 | Demographics

	Radiation (n=14)	Control (n=11)
Age	64.5	64.7
Gender	8 M, 6 F	5 M, 6 F
Ethnicity		
Caucasian	9	6
Black	5	4
Other	0	1
Years on hemodialysis (years)		
1	3	2
1–3	7	6
3–5	2	3
>5	2	0
ESRD cause		
Diabetes	7	7
Hypertension	3	3
Glomerulonephritis	1	0
Others	3	1

ESRD, end-stage renal disease; F, female; M, male.

Table 2 | Hemodialysis access history

	Radiation (n=14)	Placebo (n=11)
No. of prior accesses		
1 Prior access	13	10
2 Prior accesses	1	1
Location of current access		
Forearm	8	6
Upper arm	6	5
Configuration of current access		
Loop	11	4
Straight	3	7

Table 3 | Angiographic screen failures

Cause	Number (%)
Tandem stenoses	10 (25)
False-positive transonics flow	8 (20)
Central venous stenosis only	4 (10)
Arterial inflow stenosis only	2 (5)
Reference vein diameter > 8 mm	2 (5)
Intragraft stenosis only	3 (7.5)
Lesion length too long (> 6 cm)	4 (10)
Treatment failure	1 (2.5)
Not reported	6 (15)

Table 4 | Angiography and angioplasty comparisons

	Radiation (n=14)	Control (n=11)	P-value
Reference vein diameter	6.9 ± 1.1	6.8 ± 1.0	0.89
Pre-angioplasty stenosis	73.0 ± 7.8	74.8 ± 14.9	0.54
Lesion length (cm)	2.7 ± 1.3	1.9 ± 1.2	0.15
Percent residual stenosis	15.1 ± 9.9	8.5 ± 8.8	0.25

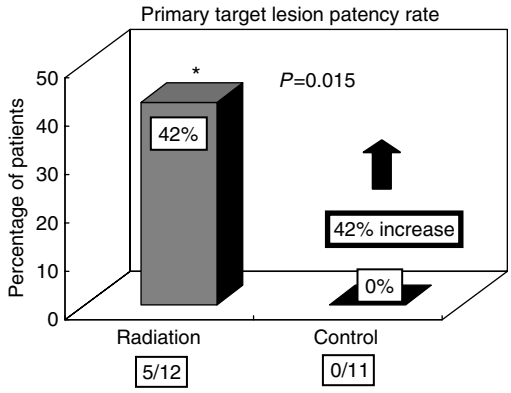

Figure 1 | Target lesion primary patency rate. Note the significant improvement with vascular brachytherapy.

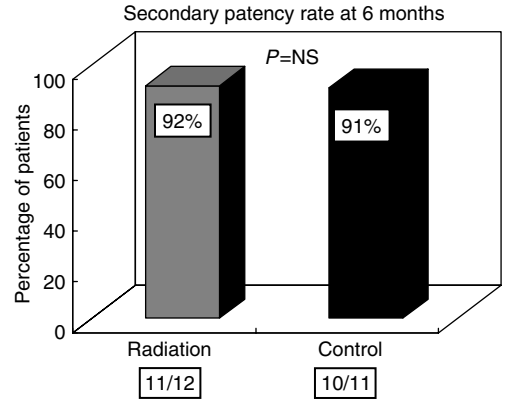

Figure 2 | Secondary patency rate at 6 months. The improvement in target lesion primary patency did not translate into a difference in secondary patency.

Screen failures

Table 3 summarizes the reasons for angiographic screen failures (see also Figure 5 for protocol algorithm). The main reasons were tandem stenoses (25%) or a false-positive Transonics blood flow (20%).

Treatment indices

Finally, there were no differences between the radiation and control groups with regard to the severity or length of stenosis of the target lesion, the response to angioplasty (residual stenosis), and the reference vessel diameter (Table 4).

Efficacy outcomes

Patients in the Radiation group had a significant improvement ($P = 0.015$; χ^2 analysis, Figure 1) in post-intervention target lesion primary patency at 6 months (41.6%) as compared to the Control Group (0%). One patient each in the Radiation and Control groups had a thrombosis of the graft that was followed by placement of a new access. There is no angiographic data in these two patients and they have been included as post-intervention target lesion primary patency failures. If these two patients are removed from the analysis, the Radiation group would have a post-intervention target lesion primary patency rate of 45% (5/11) as compared to 0% (0/10) in the Control group. One patient who was in the radiation group was found to have an arterial stenosis at the time of the 6-month angiogram with no stenosis of the target lesion. Thus primary patency of the entire dialysis access circuit in the Radiation group was 33% (4/12) as compared to 0% in the Control group ($P = 0.035$). However, this improvement in both post-intervention target lesion primary patency and post-intervention primary patency did not translate into an improvement in post-intervention secondary patency at 6 months (Figure 2) which was 92% in the Radiation group as compared to 91% in the Control group (P = NS). However, in order to achieve similar secondary patency rates at 6 months, more interventions were performed in the Control group as compared to the Radiation group (13 vs 9). Interestingly both the straight grafts (2/2) in the Radiation group did not achieve post-intervention target lesion primary patency at 6 months whereas 50% of the loop grafts (5/10) in the Radiation group did achieve this end point. In the Control group, 7/7 straight grafts did not achieve this end point as also 4/4 loop grafts. Although loop grafts appeared to do better than straight grafts in the Radiation group we believe that the numbers are far too small for any definitive analysis. Of note one patient each with a loop and straight graft died during the study. These patients have not been included.

Safety outcomes

In view of existing concerns over a possible linkage between radiation therapy and thrombosis, regardless of stenosis, we also assessed the thrombosis free rate (defined as a lack of graft thrombosis) in the two groups over the 6-month study period. The Radiation group had a thrombosis free rate at

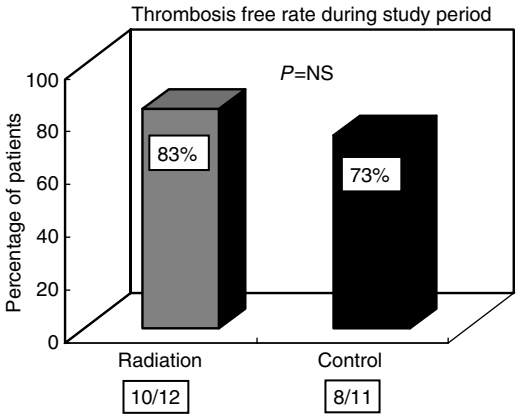

Figure 3 | Thrombosis rate during study period. There was no difference in the thrombosis rates between the two groups.

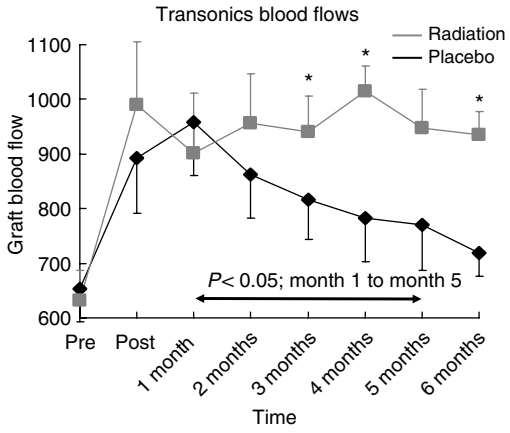

Figure 4 | Transonics blood flows. Intragraft blood flows in the Radiation group were significantly better than in the Placebo group from 3 months onwards. In addition, there was a decrement in Transonics blood flows from month 1 onwards in the Control group, which did not occur in the Radiation group.

6 months (Figure 3) of 10/12 (83%) as compared to 8/11 (73%) in the control group ($P = $ NS). Two of the three thromboses in the Control group occurred following the index angioplasty. Both occurred 63 days post-angioplasty. The third thrombosis in the Control group occurred 2 days following an angioplasty for a restenosis of the target lesion, 96 days after the index angioplasty. One thrombosis in the Radiation group occurred 2 days following the index angioplasty and radiation. This graft was abandoned. The second thrombosis in the Radiation group occurred 36 days following angioplasty for a restenotic lesion (this angioplasty was performed 31 days following the index angioplasty).

Special attention was paid to complications occurring during the interventional procedure. Four complications occurred during 88 procedures performed during the screening, treatment, and follow-up portions of the study. Three of these were in the screen failure group; a hematoma, a balloon rupture, and a pseudoaneurysm. In addition there was a small venous dissection during the screening angioplasty procedure. This patient was not included in the study.

In all 191 adverse event reports were filed during the course of this study. This included all episodes of stenosis and/or thrombosis (discussed above), which were classified as having a possible relationship to radiation. These have been discussed above. The only other adverse effect that was classified as having a possible relationship to radiation was a skin ulcer over the graft, which resulted in exposure of the graft. This occurred in a patient in the Control group. The vast majority of the adverse effects reported were related to the underlying very significant co-morbidities present in hemodialysis patients. There were no significant concerns raised about the side effect profile in either the control or radiation patients by the Data Safety Monitoring Board.

Transonics blood flow

Figure 4 summarizes the mean intragraft blood flow in the Radiation and Control groups at the time of initial screening, at the first hemodialysis session post-randomization and at monthly intervals thereafter for 6 months (or until thrombosis or stenosis). Although there were no differences between the two groups in intragraft blood flows before or immediately after angioplasty, patients in the Radiation group had significantly better blood flows at the 3- month ($P = 0.03$), 4- month ($P = 0.03$), and 6-month time points ($P = 0.005$). In addition there was an overall decline in blood flow over time in the Control group but not in the Radiation group. Specifically, there was a statistically significant difference between mean blood flow at month 1 and that at months 2 ($P = 0.014$), 3 ($P = 0.008$), 4 ($P = 0.039$), and 5 ($P = 0.018$) in the Control group. The only statistically significant result that was identified when a similar analysis was performed for the Radiation group was a difference between the month 4 and month 6 blood flows ($P = 0.044$). The clinical significance of this is unclear.

12-Month follow-up results

Although the primary end points of the BRAVO I study were at 6 months, data collection has continued after the study, and secondary patency data is available on nine patients in the Radiation group and seven patients in the Control group at 1 year post-enrollment. 44% of patients (4/9) in the Radiation group were still dialyzing through the index graft at this time as compared to 57% of patients (4/7) in the Control group.

DISCUSSION

The BRAVO I clinical trial is the first randomized study of vascular brachytherapy for the treatment of dialysis access stenosis. Although our results suggest a beneficial effect of this intervention on the primary efficacy end point of post-intervention target lesion primary patency and also on the secondary end point of post-intervention primary patency (for the entire dialysis access circuit), it is important to note that these positive effects did not translate into an improvement in secondary patency at 6 months. However,

the reduction in the number of interventions needed could potentially translate into some economic benefits at the 6-month time point. In addition, available 12-month data also does not demonstrate an increase in secondary patency (44% for Radiation vs 57% for the Controls), suggesting that radiation therapy may have only a short-lived effect or even a negative long-term effect (although our numbers at 12 months are extremely small).

A particular concern with endovascular radiation therapy has always been an increased risk of thrombotic episodes. There were no differences in thrombotic episodes between the radiation and control groups in this study. It should be noted, however, that both episodes of vascular thrombosis in the radiation group occurred following the index procedure, whereas all the thrombotic episodes in the control group occurred following a second angioplasty.

As noted in the Results section, the control group had a 0% target lesion primary patency and also 0% primary patency at 6 months. This is clearly worse than expected although previous individual studies have also reported very poor results.[9] It should be emphasized, however, that this was a randomized study and the poor results in our control group are likely to be an indicator of the complexity and poor prognosis of dialysis vascular access in hemodialysis patients, with their many concurrent morbidities.

In addition to potential efficacy, a key finding of the BRAVO I study was the demonstration of the safety of this procedure in the complex setting of uremic hemodialysis patients with PTFE dialysis grafts and significant clinical co-morbidity (two deaths during the course of the study and two further deaths during the period of continuing follow-up). Our results suggest that the safety profile of vascular brachytherapy in this population is acceptable and we believe that this is critically important information not only with regard to future larger studies, but also with regard to the off label use of this therapy in particularly recalcitrant patients who have exhausted other vascular access options.

Interestingly, the post-angioplasty Transonics blood flows were significantly better in the Radiation group as compared to the Control group from the 2-month time point onwards, owing to a stabilization of blood flow. It is unclear as to whether beneficial positive remodeling owing to radiation as reported by a number of groups was responsible for this.[33–35]

In conclusion, we believe that the BRAVO I study is an important addition to the clinical information available on anti-stenotic therapies for hemodialysis vascular access dysfunction. It must be emphasized that the BRAVO I study is a pilot study, which has demonstrated to us the possible benefits of vascular brachytherapy in the setting of dialysis access grafts. The small numbers of patients in this study, however, do not permit us to make any definitive conclusions that could have an impact on current clinical practice. However, at a minimum, we believe that the BRAVO I study has: (a) demonstrated the safety of endovascular radiation therapy in patients with dialysis access stenosis and (b) provided the background data for a larger study of radiation therapy in patients with dysfunctional dialysis access grafts.

MATERIALS AND METHODS

The BRAVO I was a randomized double blind multi-center pilot study to assess the effect of vascular brachytherapy on the 6-month post-intervention target lesion primary patency rate in hemodialysis patients with patent (non-thrombosed) but dysfunctional (decreased Transonics blood flow) grafts. Each enrolling site received Institutional Review Board and Radiation Safety Approval before consenting and enrolling patients in the trial.

Basic protocol

The basic protocol for the BRAVO I study is described in Figure 5. Full informed consent was obtained from all patients. Hemodialysis patients with patent but dysfunctional PTFE dialysis grafts, who were greater than 18 years of age, were identified on the basis of decreased intra graft blood flows using the Transonics™ device. Patients with (a) an intragraft access blood of less than 800 ml/min or (b) an intragraft access blood flow of less than 1000 ml/min, which had decreased by greater than 25% over the previous 4 months were assessed for non-angiographic exclusion criteria. These included a known hypercoagulability state, allergy, or sensitivity to anti-platelet or anti-coagulant therapy, the presence of less than two other potential access sites and the presence of a thrombosed graft or a clinical need for thrombectomy and thrombolysis. If they satisfied these criteria they were sent for an angiogram. Angiographic inclusion criteria included the presence of a single stenosis greater than 50% at the graft-vein anastomosis (target lesion), a post-angioplasty residual stenosis of less than 30%, a venous outflow injury intervention length (VOIIL) of less than 6 cm beyond the leading edge of the anastomosis and a reference vessel diameter of 4–8 cm. Angiographic exclusion criteria included tandem stenoses anywhere in the dialysis circuit from the artery supplying the graft to the right atrium or the presence of a stent at the planned treatment site. The magnitude of stenosis was determined by published reporting standards of the Society of Interventional Radiology.[36] Patients with suitable lesions initially underwent a conventional angioplasty. All lesion/vessel injury lengths were recorded by angiography in order to determine the extent of vessel injury (VOIIL), which influenced the extent (length) of subsequent radiation therapy. Patients with a residual stenosis of less than 30% who had a reference vessel diameter of less than or equal to 8 mm (no balloon size available for a larger vein; see below) and a VOIIL of less than 6 cm (in order to provide complete radiation

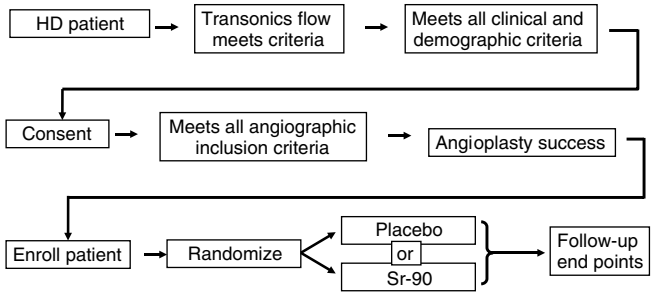

Figure 5 | Basic protocol. This algorithm for the BRAVO I study emphasizes the presence of non-angiographic (clinical) and angiographic inclusion/exclusion criteria.

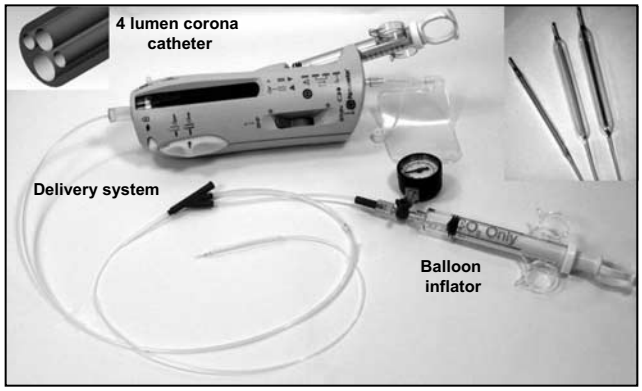

Figure 6 | Corona delivery system. The Corona delivery system consists of a plunger device (with a separate balloon inflator), which is attached to a four lumen catheter (top left inset). This ends in a special Corona balloon (see Figure 7), which is available in different sizes (top right inset).

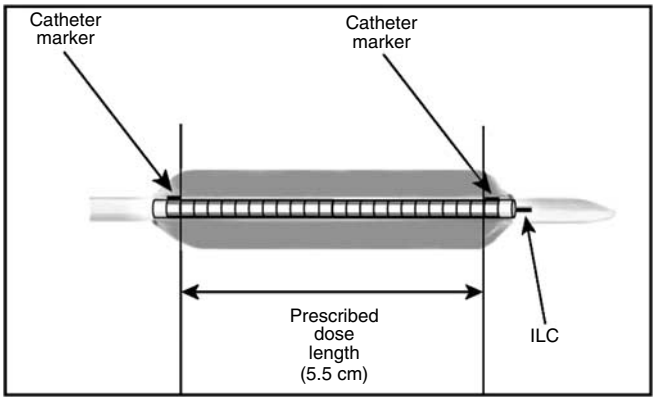

Figure 7 | Expanded representation of the corona radiation delivery balloon. Note the 60 mm long radioactive source train which is made up of twenty four 2.5 mm long strontium 90 seeds. The radioactive source train is inserted through one of the lumens once the delivery catheter balloon is in the right place (determined by the proximal and distal markers, see Figure 8).

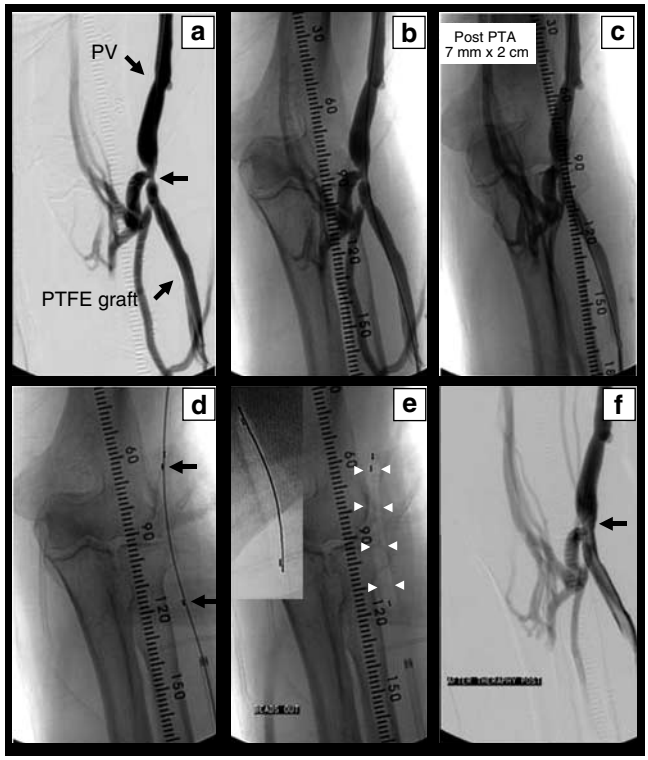

Figure 8 | Vascular brachytherapy procedure. (**a**) The typical lesion that was targeted in this study; a tight stenosis at the graft-vein anastomosis (horizontal arrow). (**b**) Following placement of the radio-opaque ruler wire a wire was passed across the stenosis. The stenotic lesion then underwent a successful angioplasty with a 7 mm ID $\times$ 2 cm long balloon. A liberal estimate of the extent of vascular injury (VOIIL) at this time would be from the 70 mm marker to the 110 mm marker (including 1 cm extra on either side). (**c**) The post-angioplasty film with the radio opaque markers. The Corona delivery catheter was then positioned so that it covered the entire region of vascular injury. (**d**) Note that the proximal and distal radiation markers are at 120 mm and 70 mm (black arrows). (**e**) The Corona balloon was then inflated (white arrowheads in post-bead removal) and the radioactive source train was introduced (inset (**e**); from different patient). Finally (**f**) A post-angioplasty, post-vascular brachytherapy film (arrow shows angioplasty site).

coverage of the area of vascular injury; see below) were randomized to receive either sham radiation therapy or vascular brachytherapy using the Novoste 'Corona' system (see below).

Vascular brachytherapy treatment

The four lumen (Figure 6, left top inset) Corona delivery system (Figure 6) that has been successfully used in the coronary setting was used for the BRAVO I study. This comprises a centering balloon catheter which uses carbon dioxide (in order to standardize radiation delivery to the vessel wall) and incorporates a four-lumen design including a 0.35 inch guide wire lumen, fluid send and return lumens, and a lumen for inflating the centering balloon with carbon dioxide. Balloon sizes from 5–8 mm were used for this study (Figure 6, top right inset). Following conventional angioplasty the carbon dioxide filled balloon was inflated to 1–2 atm and a strontium 90 radioactive source train containing 24 miniature radioactive seeds (Figure 7) was delivered to cover the entire length of balloon injury (Figures 7 and 8). Fluorescent tape markers were utilized to ensure that the entire region of vascular injury was radiated (Figure 8). The system was calibrated such that patients received a dose of 18.4 Gy, 0.5 mm into the vein wall. All patients were anticoagulated with heparin before the vascular brachytherapy procedure with the target activated coagulation time being greater than 250 s. Building upon the experience acquired from previous studies of endovascular radiation therapy and current FDA recommendations,[37] the BRAVO protocol incorporated strict guidelines to ensure that the entire area of injury was irradiated with adequate margins in order to avoid the 'candy wrapper' effect (aggressive rebound stenosis at the edges of the radiated zone) described in earlier studies of vascular brachytherapy in the coronary circulation. Specifically, patients with a VOIIL of greater than 6 cm beyond the leading edge of the graft-vein anastomosis were excluded as the maximal length of vascular injury that could be radiated in this study was 6 cm (two 5 cm length applications of the strontium 90 source with a requirement for a 1 cm overlap into graft, a 1 cm overlap between the two source train applications and a 1 cm overlap beyond the site of vascular injury). In addition patients with a reference vein diameter of >8 mm were excluded because of

the lack of a suitable Corona balloon. All patients were started onto either Aspirin (81 or 325 mg) or Plavix (75 mg) for the duration of the study in order to avoid potential problems with late thrombosis.[37]

Patients randomized to receive sham radiation therapy underwent an identical process, albeit with the delivery of a non-radioactive source train to the injury site. The identity of patient treatment was only known to the radiation physicist.

Post-procedure follow-up

Patients received clinical follow-up at their first hemodialysis session and monthly thereafter. All patients were required to return for a 6-month angiogram, unless they had already reached the study endpoint (see below). All patients also underwent monthly Transonics flow measurements and were referred for an angiogram if graft blood flow fell below 800 ml/min or if patients had a greater than 25% drop in flow with a final flow of <1000 ml/min. A detailed vascular history (all percutaneous or surgical interventions and episodes of thrombosis) following the index procedure was collected on all patients. All adverse events and hospital admissions were recorded.

Outcomes and end points

The primary efficacy endpoint of the study was post-intervention target lesion primary patency at 6 months by angiography. This was defined according to the SIR guidelines as the occurrence of access thrombosis or the need for intervention within the treatment area. The primary safety endpoint was a composite endpoint of death, emergency surgery on the graft, venous rupture, or aneurysm formation or enlargement at 6 months. Secondary endpoints included post-intervention primary patency (defined as a stenosis anywhere within the access circuit), post-intervention secondary patency defined as the surgical revison or abandonment of the access (i.e., grafts *could* undergo repeated angioplasties to keep the access patent and would not reach the secondary end point) and graft thrombosis at 6 months. Please note that primary and secondary patency do not refer to target lesion versus lesions at other places within the access circuit. In addition, Transonics blood flows were measured before angioplasty, at the first hemodialysis session post-angioplasty and at monthly intervals thereafter until the 6-month angiogram or prior intervention/thrombosis of the graft (primary patency end point). Thus the target lesion primary patency and the primary patency data were obtained in the context of angiograms being performed for decreased blood flow, and also for all patients who had not reached the primary end point at 6 months. All complications were recorded by the clinical sites. All serious adverse events were adjudicated by an independent Data Safety Monitoring Board.

Angiographic analyses

All angiograms were evaluated by a core laboratory (Montreal Heart Institute), with the radio-opaque ruler in place. (Figure 8) A dedicated brachytherapy software analysis package (Medical Imaging Systems) developed by Medis Corporation (Leiden, The Netherlands) was used. Angiograms of the successful interventional procedure were obtained in subtracted and non-subtracted images on either plain film support or recorded on compact disc in DICOM format. All images were analyzed with the radiopaque ruler in place. The purpose of this ruler was: (1) to calculate a calibration factor that allows the computer assisted package to obtain absolute measurements in millimeter, and (2) to verify the precise positioning of proximal and distal margins of each VOILL and each subsequent vascular brachytherapy treatment. These physical landmarks are part of the dedicated brachytherapy software analysis package developed by Medis Corporation and are essential to calculate relevant parameter measurements in subsegments such as injured, irradiated, and fall off zone segments. Image acquisition included non-subtracted images for recording the positioning of all balloon dilations and all brachytherapy sources. The angiographic acquisition phases with contrast material (i.e. pre-dilation, post-dilation, and final post-radiation) included at least one partially subtracted image to allow visualization of bony landmarks and of the radiopaque ruler. These angiographic images were converted into a proper file format so they could be read and analyzed with the brachytherapy analysis software. The images of interest were then displayed on a video monitor, and, by the use of an automatic edge detection program, vessel contours were determined by assessing brightness along scan lines perpendicular to the centerline of the vessel. The resulting edge strength values were input to minimal cost analysis contour-detection algorithm, which searches for an optimal contour path along the entire segment. The calibration factor calculated from the projected radiopaque ruler (pixel size ranging from 0.22 to 0.32 mm) allowed absolute measurements of the minimal lumen diameter, reference vein diameter; interpolated method), length of stenosis, length of balloon injuries (VOILL), and length as well as positioning of radiation sources.

Statistical analysis

Differences in post-intervention primary patency, post-intervention secondary patency, and post-intervention thrombosis rate were analyzed using a χ^2 analysis (StatView 5, SAS Institutes, Cary, NC, USA). Differences in Transonics blood flows between the Radiation and Control groups were analyzed using an analysis of variance test, whereas differences between Transonics blood flows at different time points within the same group (Radiation or Control) were assessed with a paired *t*-test. A *P*-value of less than 0.05 was considered to be significant.

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APPENDIX A

The BRAVO I sites that enrolled subjects included:
University of Cincinnati (Cincinnati, OH, USA) 01
Piedmont Hospital of Atlanta (Atlanta, GA, USA) 02
OSF St Francis Medical Center (Peoria, IL, USA) 03
Mayo Clinic/St Mary's Hospital (Rochester, MI, USA) 05
Louisiana State University Hospital at Shreveport (Shreveport, LA, USA) 07
Baptist Medical Center (Jacksonville, FL, USA) 12